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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 05/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/759,746	FERNANDEZ-SALAS ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application Election/Restrictions

Applicant's election without traverse of Group I and botulinum toxin type A in the reply filed on March 24, 2006 is acknowledged.

Claims 1-48 are pending. Claims 49-55 are cancelled. Election was made **without** traverse in the reply filed on March 24, 2006. Claims 1-48 are under examination in this office action.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application No. 10/163106, Application No. 09/910346, and Application No. 09/620840 fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112

for one or more claims of this application. The instant application claims a method of identifying a compound that alters a biological persistence of a Clostridial toxin comprising a test localization assay which is not presented in the Application Nos. 10/163106 filed on Jun 4, 2000, 09/910346 filed on Jul 20, 2001, 09/620840 filed on Jul 21, 2000. Therefore, the priority for the instant application is Jan 16, 2004.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see p. 25,[0097]. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claims 25, 31 and 47 are objected to as encompassing non-elected subject matter.

Claims 17 and 18 are objected to because of the following informalities: the typographical error of "inclusive". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identifying a compound that affects the localization of the light chain of Clostridial botulinum toxin type A (BoNT/A) and the cleavage activity of the BoNT/A/E light chain on SNAP25 in neuronal like cells or secretory cells, does not reasonably provide enablement for a method of identifying a compound that alters a biological persistence of Clostridial toxin as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

Claims 1-22 are drawn to a method of identifying a compound that alters a biological persistence of a Clostridial toxin by contacting the cells expressing a Clostridial toxin light chain with the test compound and evaluating the localization and enzyme activity of the light chain when compared to a negative and a positive control compounds. Claims 23-48 are drawn to a method of identifying a compound that inhibits the biological persistence of a Clostridial toxin by contacting the cells expressing a Clostridial toxin light chain with the test compound and evaluating the localization and enzyme activity of the light chain when compared to a negative and a positive control compounds. Applicant discloses that GT1b can enhance the cleavage activity of the light chain of BoNT/A on SNAP 25 and also change the cellular localization of the light chain of BoNT/A in Neuro-2A cells and SH-SY5Y cells. Applicant also discloses that GT1b can affect neurotransmitter release in Neuro-2A cells. In addition, Applicant discloses that the cleavage activity of the light chain of BoNT/A on SNAP25 is specific because the mutant form of the light chain has less cleavage activity on SNAP25. Further, Applicant discloses that the change of the localization of the light chain of BoNT/A also affects the cleavage activity of the light chain on SNAP25. However, Applicant fails to disclose what other enzyme activity/substrate/products are. Applicant only discloses that SNAP25 is the substrate for the light chained of BoNT/A or E. Applicant may also be enabled for a method of detecting substrates specific for specific types of toxins shown in the literature, for example VAMP is the specific substrate for

BoNT/B/D/F/G. However, Applicant is not enabled for all methods of detecting all enzyme activity and all enzyme substrates/products. It has been shown that the activity of BoNT relies on the cleavage activity of the light chain. The BoNT is post-translationally proteolysed to form a di-chain molecule composed of a light chain and a heavy chain. The light chain is responsible for intracellular catalytic activity to block neuroexocytosis and heavy chain is responsible for membrane translocation and neurospecific binding (see p. 555, the second paragraph to p. 557. Johnson Annu. Rev. Microbiol. 1999. 53:551-75). The molecules involved in the process of synaptic vesicle exocytosis include syntaxin, SNAP25, synaptobrevin, synaptotagmin, ATPase, NSF, adaptor SNAP family, family of Rab class of small G protein and effectors, and the family of Sec complex in the exocyst etc. There are many members in each family of adaptor SNAP, Rab class of small G protein and its effectors, and the Sec complex in the exocyst. Each molecule is assembled differently at different stages of processes during exocytosis. The machinery of synaptic vesicle exocytosis/endocytosis assembly and disassembly during the process has not well elucidated. Whether all molecules in a SNARE complex can be considered as enzyme substrates sensitive to the enzyme/proteolytic activity of the light chain of all forms of Clostridial toxin is undetermined, indicating undue experimentation is required. The specification has not provided enough guidance as to whether all molecules including all synaptosomal associated proteins, fragments, peptides, peptidomimetics or mixtures as recited in claims 21 and 31 are sensitive to enzyme activity or the cleavage activity of BoNT/A or all forms of Clostridial toxin. The prior art discloses that only synaptic associated

proteins can serve as substrates of a specific type of toxin, such as SNAP 25 is the substrate for BoNT/A. Each toxin has its own set of substrates. So far, how many molecules are involved and how/where the particular role of SNARE in regulating synaptic vesicle fusion is, and how BoNT interacts with SNARE proteins during exocytosis still have no conclusive answer. In addition, the change of the localization of light chain results in the change of the enzyme activity of the light chain. Applicant fails to provide enough guidance as to how to evaluate the localization pattern. The specification has not taught what the localization patterns are. A skilled artisan cannot contemplate what specific localization pattern to expect while evaluating the effects of test compounds. Applicant may be able to screen for a compound that affect the localization of light chain of BoNT/A on the plasma membrane. However, the specification fails to disclose what other subcellular localization are. The specification does not provide sufficient guidance as to how to evaluate what other subcellular localizations are since the trafficking/targeting of each molecules assembled in synaptic vesicle are vary. The instant specification is not enabling for identifying all compounds that alter/inhibit all biological persistence of all Clostridial toxins by evaluating all enzyme activity/substrates/products. Without such guidance, what localization, enzyme activity/substrates/products of the light chain of a Clostridial toxin to be evaluated, whether the test agents can regulate all localizations, enzyme activity/substrates/products of the light chain of all Clostridial toxin are unpredictable indicating that undue experimentation is required for those skilled in the art to use the invention. Therefore, in view of the necessity of experimentation, the limited working

examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method of identifying a compound that alters/inhibits a biological persistence of a Clostridial toxin by contacting the cells expressing a light chain of a Clostridial toxin and evaluating the localization, enzyme activity of the light chain of a Clostridial toxin.

Claims 1-48 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. Claims are directed to a method of identifying a compound that alters/inhibits the biological persistence of a Clostridial toxin by contacting the cells expressing the light chain of a Clostridial toxin and evaluating the localization and enzymatic activity of the light chain of a Clostridial toxin. Applicant fails to specify/describe the genus of the characteristics of enzymatic activity/enzymatic substrates/ enzyme products recited in claims 21 and 31. In addition,

Applicant is not in possession of all enzyme substrates/products as recited in the claims 21 and 31 since it is still not clear how many molecules are involved in vesicle exocytosis/endocytosis. Applicant may be in possession of the fragments or peptides of SNAP25 or VAMP that have been shown to be substrates for BoNT/A or BoNT/B/D/F/G in the art, such as the ones disclosed in US Patent Nos. 5965699 and 6762280. However, Applicant is not in possession of all fragments, peptides, peptidomimetics or mixtures as substrates for all Clostridial toxins. Applicant has not taught the specific structure/characteristics of the genus of fragments, the genus of peptides, the genus of peptidomimetics and the genus of mixtures for substrates of any toxin. One of skill in the art cannot envision what particular structures/characteristics are required for evaluating the enzymatic activity/enzyme substrates/enzyme products. Since the structure/characteristics of these enzyme activity/substrates/products are not known, a skilled artisan can not contemplate what effects of compounds on the light chain of Clostridial toxin and what characteristics of enzyme activity/substrates/products to evaluate while using the claimed invention. In addition, Applicant is not possession of all negative and positive control compounds that have no effects or have effects of changing the localization/enzyme activity of the light chain of Clostridial toxin. Applicant only provides limited species for positive control compounds and no species for negative control compounds. Applicant fails to specify/describe the particular characteristics/structure of the genus of the negative control compounds and the genus of positive control compounds are required for evaluating the localization and enzyme activity/substrate/product of BoNT/A. A skilled artisan cannot envision what compounds

can be used as a positive/negative control to evaluate whether the test compound has specific effects on the localization and enzyme activity and what specific characteristics of the enzyme activity/substrates/products are required for evaluating the effectiveness of the test compounds. The specification fails to define a particular conserved structure for a negative/positive control compound or compound derivative that is required for affecting localization and enzyme activity/substrates/products of the light chain of Clostridial toxin. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of negative/positive control compounds. The skilled artisan cannot envision all contemplated possibilities recited in the instant claims. Since the structure/characteristics of these control compounds and characteristics of enzyme activity/substrates/products are not known, a skilled artisan can not contemplate the functional correlations of these compounds and localization and characteristics of enzyme activity/substrate/product of the light chain of BoNT/A. Adequate written description requires more than a mere statement that it is part of the invention. A description of a genus of polypeptides/ compounds may be achieved by means of a recitation of a representative number of polypeptide sequences/chemical groups, defined by amino acid sequence/chemical structure, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with

reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Therefore, a method of identifying a compound that alters/inhibits the biological persistence of a Clostridial toxin by contacting the cells expressing the light chain of Clostridial toxin and evaluating the localization and enzymatic activity of the light chain of Clostridial toxin has not met the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-48 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to detect and evaluate.

Claims 1-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "alters" in claim 1 is a relative term which renders the claim indefinite. The term " alters" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant fails to set for the metes and bounds of what is encompassed within the definition of "alters". Since the metes and bounds are not unknown, a skilled artisan can not contemplate what to expect as recited in the claim. Thus the claim is indefinite.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "less" in claim 4 is a relative term which renders the claim indefinite. The term " less" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant fails to set for the metes and bounds of what is encompassed within the definition of "less". Since

the metes and bounds are not unknown, a skilled artisan can not envision how much change is considered as "less" localized as recited in the claim. Thus the claim is indefinite.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant fails to specify what amount is considered as effectively. The specification fails to metes and bounds of the amount. Thus the claim is indefinite. Applicant fails to teach what is required to establish an identifiable localization pattern". Since the metes and bounds are not unknown, a skilled artisan can not contemplate what to expect as recited in the claim. Thus the claim is indefinite.

Claims 22 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant has not defined what is encompassed within the "GFP-SNAP assay". SNAP is an abbreviation of Soluble NSF Attachment Protein. There are many members in SNAP, such as SNAP25 or SNAP23. In addition, there are many compounds affecting synaptic transmission also named SNAP, for example, SNAP-5114, a selective inhibitor of GABA transporter 3. Applicant fails to specify what is encompassed in the definition of GFP-SNAP assay; therefore, the metes and bounds of the claimed invention cannot be determined. Thus the claim is indefinite.

Claims 16- 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "enhancement" in claim 16 is a relative term which renders the claim indefinite. The term " enhancement" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant fails to set for the metes and bounds of what is encompassed within the definition of "enhancement". Since the metes and bounds are not unknown, a skilled artisan can not contemplate what to expect/determine the enhancement processing as recited in the claim. Thus the claim is indefinite.

Obviousness-Type Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-48 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 60 of copending Application No. 10732703 ('703) in view of Herreros et al. (Mol. Biol. Cell. 2001. 12: 2947-2960). Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims encompass a method of identifying a compound that alters a biological persistence of a Clostridial toxin by contacting a cell expressing the light chain of Clostridial toxin and evaluating the localization and enzyme activity of the light chain of Clostridial toxin. The claim of '703 encompasses a method of identifying a compound that alters the internalization of a Clostridial toxin into a cell by screening the compound that alter the affinity of the Clostridial toxin for lipid rafts. While not identical, the claims of the instant application and the copending application encompass same scope of invention in view of identifying a compound that alters the a biological persistence of a Clostridial toxin and localization of the Clostridial toxin. Herrerors et al. teach that both Tetanus (TeNT) and BoNT block neurotransmitter release by interacting with a complex constituted lipid and protein receptors (p. 2947, second column, second paragraph). Herrerors et al. further teach that lipid rafts are microdomains of the plasma membrane enriched in sphingolipids, cholesterol. And glycosylphosphatidylinositol (GPI)-anchored proteins and they play important roles in vesicular sorting, trafficking and signaling. Herrerors et al. teach that the heavy chain of TeNT is associated with a GPI-anchored protein, Thy-1 by FRET and immuoprecipitation (p. 2948, 2nd-3rd

paragraphs). It is known in the art that the light chain of Clostridial toxin plays an important role in intracellular activity and localization of Clostridial toxin. In addition, it is known in the art that the change of the localization of the light chain of Clostridial toxin subsequently results in the change of enzymatic activity of Clostridial toxin. A Clostridial toxin is composed of a heavy chain and a light chain. The heavy chain is responsible for the neuronal surface binding and translocation. The light chain is responsible for the proteolytic activity to block neurotransmitter release. The enzyme activity and localization of the light chain rely on internalization or endocytosis of the Clostridial toxin. It has been shown that lipid rafts are specialized domains for binding and internalization of toxins. The biological persistence of a Clostridial toxin is an inherent result due to the change of localization and enzymatic activity of the light chain of Clostridial toxin. Thus, it would have been obvious for one of ordinary skill in the art to screen a compound that alters a biological persistence of a Clostridial toxin by contacting the cells expressing the light chain of BoNT/A with a test compound and evaluating the enzyme activity and localization of the light chain since the enzyme activity and localization of the light chain rely on the internalization of toxin. One of ordinary skill in art would have been motivated and expected success in screening a compound that alters/inhibits a biological persistence of a Clostridial toxin by evaluating the localization and enzymatic activity of the light chain of the toxin because affecting the internalization of a toxin by altering binding affinity to lipid rafts for toxin internalization would affect the biological persistence of the toxin. In addition, the biological persistence of a toxin is mainly dependent on the binding of the heavy chain

to lipid rafts for internalization and the enzymatic activity of light chain. Thus the instant and copending Application claim the same and non-distinct inventions of a method of identifying a compound that alters the biological persistence of a Clostridial toxin by evaluating the localization and enzymatic activity of a Clostridial toxin or affecting the internalization of a Clostridial toxin.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23-32 are rejected under 35 U.S.C. 102 (b) as being anticipated by US Patent No. 5965699 (Schmidt et al. issued on Oct 12, 1999, effective filing date Nov 6, 1996).

US Patent No. 5965699 ('699) teaches a method for screening a compound that inhibiting/activating botulinum toxin type A. '699 teaches using a HPLC assay and fluorescamine assay to analyze the enzyme/proteolytic activity of BoNT/A (see column

12 line 43 to column 13, line 25). '699 teaches the synthetic peptides corresponding residues of 187-201 of SNAP25 labeled with fluorescence can serve as substrates for light chain of BoNT/A to analyze the proteolytic activity of the light chain by a specific fluorescence spectrophotometer (see column 13, lines 1-25).'699 further teaches using the method of detecting the proteolytic activity of BoNT/A to screen a compound that inhibits/activates BoNT/A (see column 50, claim 9). '699 teaches different concentrations, positive and negative controls (see column 5. lines 55-67). In addition, the positive/negative controls are routine controls that would not render the invention patentable. Therefore, claims 23-32 are anticipated by US Patent No. 5965699.

Claims 23-32 are rejected under 35 U.S.C. 102 (e) as being anticipated by US Patent No. 6762280 (Schmidt et al. issued on Jul 13, 2004, effective filing date Sep 25, 2000).

US Patent No. 6762280 ('280) teaches a method for identifying a compound that inhibits/enhances the proteolytic activity of botulinum neurotoxin serotype A (BoNT/A) by incubating neurotoxin with the test compound and a fluorescence labeled substrate, and measuring the fluorescence signal resulting from proteolytic cleavage of the substrate by neurotoxin (see column 15, Examples1-2 and column 25, claim 9). '280 teaches using the fluorescence labeled peptide substrates to detect the proteolytic activity of the BoNT/A through its catalytic domain, which is the light chain of BoNT/A by a FRET/ELISA assay or antibody detecting assay (see column 4 line 37 to column 5, line 19). '280

further teaches using the FRET assay of detecting the proteolytic activity of the light chain of BoNT/A and ELISA method to screen a compound that inhibits/enhance the proetolytic activity of the light chain of BoNT/A (see column 9, line 65 to column 10, line 36). The results are compared with the tests of controls (see column 12, lines 57-61). '280 also teaches different concentration, positive/negative controls (see column 14, lines 14-24), and the labeling method as well as detecting methods (see column 4 line 37 to column 5, line 19). In addition, the positive/negative controls are routine controls that would not render the invention patentable. The reference meets the limitations of the claims; therefore, claims 1-48 are anticipated by US Patent No. 6762280.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6762280 (Schmidt et al. issued on Jul 13, 2004, effective filing date Sep 25, 2000) in view of Fernandez-Salas et al. (Society for Neuroscience Abstract Viewer and Itinerary Planner, 2003. Vol 2003, pp. Abstract No. 9.2., Plasma membrane localization signals in the light chain of botulinum neurotoxin serotype A, 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003) or Steward et al. (Naunyn-Schmiedeberg's Archives of Pharmacology, (June 2002) Vol. 365 No. Supplement 2, pp. R19., Localization of BoNT light chains in neuronal and non-neuronal cell lines, implications for the duration of action of the different serotypes. International Conference on Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins. Hannover, Germany, June 08-12, 2002 CODEN: NSAPCC. ISSN: 0028-1298).

US Patent No. 6762280 teaches as set forth above but fails to teach evaluation of the localization of light chain of a Clostridial toxin.

Fernandez-Salas et al. teach that the fusion protein of the light chain of BoNT/A to GFP protein is colocalized with SNAP25 when transfected in neurons. The colocalization can be detected by confocal microscopy (see the Society for Neuroscience Abstract).

It would have been obvious for one of ordinary skill in the art at the time of the instant invention was made to combine the teachings of US Patent No. 6762280 and Fernadez-Salas et al. to screen a compound that affects a biological persistence of a Clostridial toxin by evaluating the localization and enzymatic activity. The person of ordinary skill in the art would have been

motivated to make those modifications because the persistence of proteolytic activity of a Clostridial toxin relies on the light chain domain of the toxin. In addition, the specific substrate for BoNT/A is SNAP25, which is one of SNARE complex involved in exocytosis of synaptic vesicles. A Clostridial toxin is composed of one heavy chain and one light chain. The interaction of BoNT/A with its substrate, such as SNAP25, is intracellular cleavage on SNAP25 and subsequently inhibits exocytosis of synaptic vesicles. The internalization of BoNT/A is to bring the molecule to interact with SNAP25. Therefore, one of ordinary skill in the art would have expected success in screening a compound that alters/inhibits a biological persistence of a Clostridial toxin by contacting cells expressing a light chain to a Clostridial toxin and evaluating the localization and proteolytic activity of the light chain.

Claims 1-48 are provisionally rejected under 35 U.S.C. 103(a) as being obvious over copending Application No. 10732703 (US20050129677) which has a common Inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if published or patented. This provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future publication or patenting of the conflicting application. Claims 1-48 are provisionally as being obvious over copending Application No. 10732703 in view of Herreros et al. (Mol. Biol. Cell. 2001. 12: 2947-2960). The reasons are provided in the section of Obviousness-Type Non-Statutory Double Patenting.

This provisional rejection might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application prior to the effective U.S. filing date of the copending application under 37 CFR 1.131. This rejection might also be overcome by showing that the copending application is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Conclusion

NO CLAIM IS ALLOWED.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Vaidynanthan et al. Proteolysis of SNAP25 isoforms by botulinum neurotoxin types A, C, and E: domains and amino acid residues controlling the formation of enzyme-substrate complexes and cleavage. J. Neurochemistry. 1999. 72. 327-337.

Anderson et al. A role for lipid shells in targeting proteins to caveoloae, rafts, and other lipid domains. Science 2002. 296: 1821-1825.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
April 24, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER